DESIGN OF OBSERVATIONAL STUDIES

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I. Introduction - Types of Study Designs

   A. Observational vs. experimental

   B. Controlled vs. uncontrolled

   C. Hierarchy of study designs: case reports, case series, cross-sectional surveys, case-control studies, prospective studies, clinical trials

II. Case Reports [Example: CDC. Pneumocystis pneumonia-- Los Angeles. MMWR 1981; 30:250-2.]

   A. Object: To make observations about medical phenomena in single patients

   B. Design: Simple description of clinical data without comparison group

   C. Observations should be comprehensive and adequately detailed

   D. Presentation of findings: as needed to illustrate the phenomenon

   E. Analysis: None

   F. Interpretation/Conclusion:

      1. What observations have been made prior to this report?

      2. What new phenomenon is illustrated?

      3. What further studies should be done?

   G. Advantages

      1. Inexpensive and easily done

      2. Helpful in hypothesis formation

   H. Disadvantages

1. Biased selection of subjects so that conclusions are difficult to generalize

2. Were the findings a chance happening or a characteristic of the disease?

III. Case Series [Example: Gottlieb et al. Pneumocystis carinii pneumonia and mucosal candidiasis in previously healthy homosexual men. N Engl J Med 1981; 305:1425-31.

A. Object: To make observations about patients with defined clinical characteristics (e.g., patients with a certain disease or cluster of symptoms)

B. Design: Simple description of clinical data without comparison groups, the data derived from a well-defined group of individuals

C. Observations:

1. Should have clear definitions of phenomena being studied

2. These same definitions should be applied equally to all individuals in the series

3. All observations should be reliable and reproducible

D. Presentation of findings

1. Proportions (%, per 10^5, etc) of the study population with the phenomenon

2. Mean or median levels of relevant factors in the population

3. Important subgroups that may need separate data presentation (by sex, age, etc.)

E. Analysis

1. Means, standard errors for continuous variables

2. Proportion positive for noncontinuous data, confidence limits around proportions

F. Interpretation/Conclusion

1. Description of study group according to these characteristics

2. Is the study group representative of all patients with this disorder-- Can conclusions be generalized?

G. Advantages

1. Useful in hypothesis formation, natural history studies, describing "clinical experience"

2. Easy and inexpensive to do in hospital settings

H. Disadvantages: Biased selection of study patients may lead to inability to generalize study results. Were only the sickest or most typical patients included in the study?

IV. Prevalence Surveys or Cross-Sectional Studies [Example: Detels et al. Relation between sexual practices and T-cell subsets in homosexually active men. Lancet 1983; 1:609-11.

A. Object: To make observations concerning the prevalence and characteristics of a disease in a well-defined population over a defined period of time (period prevalence)

B. Design

1. Define the population under study

2. Derive a sample of the population

3. Define the characteristics being studied, including "cases" and "controls"

C. Observations

1. Should be standardized and clearly defined

2. Methods of data collection should be applied equally to all study participants

D. Presentation of findings

1. Prevalence (%, cases per 10^5, etc.) for the observation in the population

2. Mean or median levels of relevant factors in the population

3. Important subgroups may need separate data presentation (e.g., age, race, sex)

E. Analysis: See case-control study discussion below

F. Conclusions

1. Descriptive:

a. What are the characteristics of the group of interest (those with disease, of given age, etc.) in the population?

b. How common is the factor of interest (disease, risk factor, etc.) in the study population?

c. What are the distributions of factors of interest (age, blood pressure, vital capacity, etc.) in the study population?

3. Associative:

a. What are the relationships of the factors of interest to other factors in the study population?

b. How do persons with the factor of interest differ from those without it?

G. Advantages

1. Inexpensive for common diseases

2. Provide more representative cases than do case series

3. Relatively short duration of the study

4. Can be addressed to specific populations of interest

5. Can examine wide variety of factors simultaneously

H. Disadvantages

1. Unsuitable for rare diseases or diseases of short duration (prevalence = incidence x duration)

2. Several types of bias may be operative (see case-control discussion below)

3. High refusal rate may make accurate prevalence estimates impossible

4. Generally more expensive and time-consuming than case-control studies (see below)

5. The disease process may alter measurements of related factors and no data are collected regarding the temporal relationship between the measured factors and the development of disease

V. Case-Control or Retrospective Studies [Example: Jaffe et al. National case-control study of Kaposi's sarcoma and Pneumocystis carinii pneumonia in homosexual men: Part 1. Epidemiologic results. Ann Intern Med 1983; 99:145-51.]

A. Object: To make observations regarding possible associations between a disease and one or more hypothesized risk factors

B. Design

1. General strategy: To compare the prevalence or level of the possible risk factor between a representative group of diseases subjects (cases) and a representative group of disease-free subjects derived from the same population

Disease		No Disease	
Exposed	Non-Exposed	Exposed	Non-Exposed

2. Basic assumptions

a. Cases are representative of all patients who develop the disease

b. Controls are representative of the general "healthy" population who do not develop the disease

c. Information is collected from cases and controls in the same way

3. Selection of cases

a. Should have standardized selection criteria from a well defined, homogeneous population

b. Sources: case registries, admission records, pathology logs

c. Aim for as high a participation rate as possible

4. Selection of controls-- the most difficult issue

a. The perfect control group probably doesn't exist

b. Must have standard selection criteria from a well defined homogeneous

population

c. Sources: sample of general population, neighborhood, families

d. Cost and assessibility should be considered in the selection of controls

e. Multiple control groups; for example, one hospital control and one neighborhood control per case, are considered to be methodologically superior to assure that the observed associations are not spurious

5. Adjustment of the results in the analysis phase can be done if subgroups are large enough

C. Observations: Data are collected "looking back" for possible exposures

1. The factors observed and the conditions during the observation should be specified

2. All observations made using the same methods in cases and controls

3. Validity of measurement techniques should be established

D. Potential sources of bias: Selection and observation

1. Types of selection bias

a. Prevalence-incidence bias: A late look at those exposed or affected early will miss fatal episodes, transient episodes, mild or silent cases, or cases in which evidence of exposure disappears with disease onset

b. Nonrespondent bias: Persons unwilling or unable to respond may have exposures or outcomes which differ from respondents'

c. Membership bias: Membership in a group may imply a degree of health which differs systematically from that of the general population

d. Diagnostic suspicion bias: Knowledge of the subject's prior exposure to a putative cause may influence both the intensity and outcome of the diagnostic process

2. Types of observational or interviewer bias

a. Exposure suspicion bias: Knowledge of the patient's disease status may influence both the intensity and outcome of a search for exposure to a putative

cause

b. Recall bias: Questions about specific exposures may be asked several times of cases but only once of controls

c. Family information bias: The flow of family information about exposures and illnesses is stimulated by, or directed to, a new case in its midst

E. Presentation of findings: The 2 X 2 table

	Presence of Disease		
Characteristic	Number with Disease	Number with-out Disease	Total
Present	a	b	a + b
Absent	c	d	c + d
Total	a + c	b + d	N

F. Analysis

1. Proportion of cases exposed (a/a+c) can be compared with the proportion of controls exposed (b/b+d) by Chi square or Fisher's exact tests

2. For continuous variables (especially in cross-sectional studies), mean levels of cases can be compared with those of controls using Student's t test, nonparametric tests, etc.

3. Measures of association; the odds ratio

a. Odds are related to probability: odds = p/(1-p)

1. If probability of horse winning race is 50%, odds are 1/1

2. If probability of horse winning race is 25%, odds are 1/3 for win or 3 to 1 against win

3. If probability of person developing disease is a/(a+c), odds are:

$$\frac{a/(a+c)}{\quad}$$

$$1-[a/(a+c)]$$

which, multiplied by $\frac{(a+c)}{(a+c)}$, equals

$$\frac{a}{(a+c)-a} = \frac{a}{c}$$

b. The odds that a diseased person was exposed (a/c) is compared with the odds that a nondiseased person was exposed (b/d); this equals:

$$\text{Odds Ratio} = \frac{a/c}{b/d} = \frac{ad}{bc}$$

c. More familiar measure of association is relative risk, which is risk in exposed [a/(a+c)] divided by risk in unexposed [b/(b+d)]:

$$\text{Relative Risk} = \frac{a/(a+c)}{b/(b+d)}$$

d. If the disease to be studied is rare, a is small compared to c and b is small compared to d, so a and b contribute little to the denominators of a/a+c and b/b+d. As a and b approach 0, a+c approaches a, while b+d approaches d, so the odds ratio may be written:

$$\text{Odds Ratio} = \frac{a/(\sim c)}{b/(\sim d)} = \frac{ad}{bc}$$

e. The odds ratio estimates the relative risk well if the disease is rare

G. Advantages of a case-control study

1. May be the only way to study the etiology of rare diseases

2. Can study multiple etiologic factors simultaneously

3. May be less time-consuming and expensive

4. If assumptions are met, associations and risk estimates are consistent with other types of studies

H. Disadvantages of a case-control study

1. Does not estimate incidence or prevalence

2. Relative risk is only indirectly measured

3. Both selection and information biases may give potentially spurious evidence of association between a factor and a disease
4. Usually cannot study rare exposures

5. Temporal relationship between exposure and disease can be difficult to document

VI. Prospective or Longitudinal Cohort Studies [Example: Jaffe et al. The acquired immuno-deficiency syndrome in a cohort of homosexual men. A six-year follow-up study. Ann Intern Med 1985; 103:210-214.]

A. Object: To make observations concerning the association between a given exposure (risk factor) and subsequent development of the disease

B. Study Design

1. Overall strategy: To identify a homogeneous group of persons exposed to a purported risk factor and a second similar group of persons not exposed to the risk factor. Both groups are then followed forward in time to compare incidence rates between exposed and nonexposed.

2. Types of Prospective Studies

a. Concurrent prospective study (longitudinal study): a defined population at present is surveyed to identify exposed and nonexposed individuals who are followed forward in time (e.g., several years) to define incidence rates

b. Nonconcurrent prospective study (retrospective cohort study): a defined population has had the presence or absence of exposure ascertained in an

accurate, objective fashion in the past and is surveyed at present for occurrence of disease to allow definition of incidence rates in exposed and nonexposed

TIMEFRAMES FOR HYPOTHETICAL CONCURRENT AND NONCONCURRENT PROSPECTIVE STUDIES CONDUCTED IN 1994

Concurrent					Non-Concurrent
1994		Defined Population			1974
2004	Exposed		Non-Exposed		1984
2014	Disease	No Disease	Disease	No Disease	1994

3. Assumptions

   a. The exposed and nonexposed groups are representative samples of a well-defined general population

   b. The absence of "exposure" should also be well defined and is assumed to be maintained in the non-exposed group during the course of the study

C. Observations

1. Definitions of disease outcome should be well determined prior to the study's inception and should not be changed during the course of the study

   a. Endpoints may vary in "hardness", e.g., from death to subjective symptoms

   b. Standard criteria should be applied to both exposed and nonexposed groups, i.e., there should be no bias in determining outcomes in exposed vs. nonexposed

2. Definitions of disease should be reliable and reproducible

3. Every effort should be made to minimize the "lost to follow-up" rate since large nonresponse rates (> 20%) raise questions as to the accuracy of incidence rates in exposed and nonexposed groups

D. Presentation of findings: The 2 X 2 table

	Presence of Disease		
Characteristic	Number with Characteristic	Number without Characteristic	Total
Present	a	b	a + b
Absent	c	d	c + d
Total	a + c	b + d	N

E. Analysis of Data

1. Incidence rates for the study period (e.g., 3 years) in the exposed (a/a+b) and in nonexposed (c/c+d) are compared by Chi square or Fisher's exact tests

2. Measure of association: What is the relative risk of exposed developing the disease compared to the nonexposed?

$$\text{Relative Risk} = \frac{\text{Incidence in exposed}}{\text{Incidence in non-exposed}} = \frac{a/a+b}{c/c+d}$$

3. May wish to calculate confidence limits (e.g., 95%) around relative risk estimate

4. If variable lengths of follow-up are present, may wish to use life table methods or use person-years to calculate incidence rates (# cases per 100 person-years of follow-up)

F. Conclusions

1. To what larger groups can the results be generalized?

2. Is the association significant? Is the association strong?

G. Advantages of the prospective study

1. Cases are incident cases and may be more representative of cases than in retrospective studies

2. Design provides more information about the natural history of the disease

3. Incidence rates are available

4. Relative risk is directly estimated

5. Fewer sources of bias than retrospective studies

6. Many diseases can be studied with regard to their relationship to the exposure

7. Temporal relationships between exposure and disease firmly established

8. Best to study effects of rare exposure with frequent cases among the exposed

H. Disadvantages

1. Duration of the study may be exceedingly long, making difficult the maintenance of consistent study methods and enthusiasm of the staff

2. Follow-up of free-living populations may be very expensive

3. Large populations often required

4. Exposures can be studied only if baseline data are available

5. Rare diseases cannot be studied

6. Several types of bias may produce spurious association (bias of assessment, loss to follow-up)

VII. Inference in observational studies - Is the association causal?

A. Statistical significance

B. Strength of the association (odds ratio, relative risk)

C. Dose-response relationships

D. Temporal sequence

E. Consistency of the association (internal "validity")

F. Replication of results (external validity)

G. Biologic plausibility

H. Experimental evidence

References (examples of major types of epidemiologic studies in AIDS):

1. Case report

   CDC. Pneumocystis pneumonia-- Los Angeles. MMWR 1981; 30:250-2.

   Initial report of five cases of pneumocystis pneumonia in previously healthy, homosexual men.

2. Case series

   Gottlieb MS, Schroff R, Schanker HM, Weisman JD, Fan PT, Wolf RA, Saxon A. Pneumocystis carinii pneumonia and mucosal candidiasis in previously healthy homosexual men. N Engl J Med 1981; 305:1425-31.

   Detailed description of four previously healthy homosexual men with P carinii pneumonia, mucosal candidiasis and other opportunistic infections, first implication of new acquired cellular immunodeficiency.

3. Cross-Sectional Study
   Detels R, Fahey JL, Schwartz K, Greene RS, Visscher BR, Gottlieb MS. Relation between sexual practices and T-cell subsets in homosexually active men. Lancet 1983; 1:609-11.

   Prevalence of decreased T4/T8 ratio in 89 young, non-ill, homosexually active men in Los Angeles, correlated with specific forms of sexual behavior.

4. Case-Control or Retrospective Studies

   Jaffe HW, Choi K, Thomas PA, Haverkos HW, Auerbach DM, Guinan ME, Rogers MF, Spira TJ, Darrow WW, Kramer MA, Friedman SM, Monroe JM, Friedman-Kien AE, Laubenstein LJ, Marmor M, Safai B, Dritz SK, Crispi SJ, Fannin SL, Orkwis JP, Kelter A, Rushing WR, Thacker SB, Curran JW. National case-control study of Kaposi's sarcoma and Pneumocystis carinii pneumonia in homosexual men: Part 1. Epidemiologic results. Ann Intern Med 1983; 99:145-51.

   Study of 50 cases and 120 matched homosexual male controls in New York City, San Francisco, Los Angeles and Atlanta. Identified several risk factors related to sexual behavior, determined strength and independence in multivariate analysis.

5. Prospective or Longitudinal Cohort Study

Jaffe HW, Darrow WW, Echenberg DF, O'Malley PM, Getchell JP, Kalyanaraman VS, Byers RH, Drennan DP, Braff EH, Curran JW, et al. The acquired immunodeficiency syndrome in a cohort of homosexual men. A six-year follow-up study. Ann Intern Med 1985; 103:210-214.

Prospective study of 6875 homosexual men from San Francisco City Clinic between 1978 and 1980. Determined incidence and prevalence of the acquired immunodeficiency syndrome, related conditions, and infection with the human T-lymphotropic virus.

6. Clinical Trial

Wharton JM, Coleman DL, Wofsy CB, Luce JM, Blumenfeld W, Hadley WK, Ingram-Drake L, Volberding PA, Hopewell PC. Trimethoprim-sulfamethoxazole or pentamidine for Pneumocystis carinii pneumonia in the Acquired Immunodeficiency Syndrome. Ann Intern Med 1986; 105:37-44.

Forty patients with AIDS assigned at random to receive TMP-SMX or pentamidine for first episode of P. carinii pneumonia.

DESIGN OF OBSERVATIONAL STUDIES

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Lecture Assessment

1. What basic assumptions are necessary for results of case-control studies to be valid?

    a. Cases are representative of all patients who develop the disease

    b. Controls are representative of the general "healthy" population who do not develop the disease

    c. Information is collected from cases and controls in the same way

    d. All of the above

2. Which study design is best suited to identifying potential etiologic factors for a rare disease?

    a. Case series

    b. Cross-sectional studies

    c. Case-control studies

    d. Prospective observational studies

3. Which study design is best suited to identifying potential etiologic factors for a variety of common diseases?

    a. Case series

    b. Cross-sectional studies

    c. Case-control studies

    d. Prospective observational studies

4. Which of the following provides the strongest evidence for a causal association in observational studies?

    a. Strength of the association (odds ratio, relative risk)

b. Dose-response relationships

c. Temporal sequence

d. Consistency of the association (internal "validity")

5. (from Hennekens and Buring, Epidemiology in Medicine, Little, Brown and Co., Boston, 1987)

A case-control study was conducted to evaluate the interrelationships between several risk factors for myocardial infarction. Information on smoking status was collected from a total of 789 cases and controls. Current cigarette smoking, defined as smoking within the past three months, was reported by 157 of the 366 cass and 110 of the 423 controls. Set up the appropriate two-by-two table and calculate a measure of association between current smoking and myocardial infarction.